Settling the Score with Scleroderma While Waiting for a Cure:

Addressing Disease Progression in New Clinical Trials

Scleroderma, also called systemic sclerosis (SSc), is a rare, progressive autoimmune connective tissue disorder with no cure. It causes inflammation in the skin and other parts of the body and triggers the immune system to produce excess collagen, which leads to hardening and tightening of skin and tissue (*i.e.*, fibrosis). It is a heterogeneous disease that affects all patients differently, manifesting as limited (*i.e.*, progressing more slowly) and diffuse (*i.e.*, more advanced). The average age of disease onset is 30–50 years, and four out of five patients with scleroderma are women, according to the Scleroderma Research Foundation (SRF).[1] The Johns Hopkins University, host to one of several designated scleroderma research and treatment centers in the United States (US), notes that approximately (~) 300,000 people in the US have been diagnosed with scleroderma, and ~10,000 die from the most serious forms of the disease each year.[2]

The US Food and Drug Administration (FDA) has increased its focus on specific disease areas, including rare diseases, and has been seeking input on what patients are hoping for when considering treatment options. Recognising the value of gathering patient input, the agency hosted several disease-specific patient-focused drug development (PFDD) public workshops after the passage of the fifth reauthorisation of the Prescription Drug User Fee Act (PDUFA V). In October 2020, the FDA held one such workshop to obtain patients' perspectives on scleroderma, including effects on their health and well-being that most impact daily life and their experiences using prescription medical treatments and other treatments or therapies.[2] Presentations at the meeting provided an overview of scleroderma, including the pathogenesis of the disease, which is not fully understood. However, over the past few decades, progress has been made in understanding its pathogenesis, which includes vascular involvement or vasculopathy (*e.g.* Raynaud's phenomenon), dysregulation of the immune system, and fibrosis in the skin, musculoskeletal system, and internal organs (*e.g.*, lungs, heart, kidneys).

Treatments generally address the symptoms of scleroderma and do not target the underlying cause of the disease. Typical therapies include proton pump inhibitors for digestive symptoms, medications to prevent organ rejection and/or treat arthritis (*e.g.*, immunosuppressants), corticosteroids for skin and arthritis symptoms, blood pressure medications, and pain relievers. None of these treatments reverse the disease or halt its progression.

Historically, drug development for scleroderma has focused on reducing the severity of symptoms and managing or preventing challenges associated with disease progression. Interstitial lung disease (ILD) – a complication caused by scleroderma in ~40–75% of all patients with the disease – is the leading cause of death in this population.[4] Scleroderma-associated ILD (SSc-ILD) has been and continues to be treated off label with immunosuppressive agents (*e.g.*, mycophenolate mofetil, mycophenolic acid). However, in 2019, the FDA approved the first treatment for SSc-ILD, Ofev (nintedanib), from Boehringer Ingelheim Pharmaceuticals, Inc. The product is indicated to slow the rate of decline in pulmonary function in patients with SSc-ILD. A second therapeutic for that same indication came to market in 2021 when the agency approved tocilizumab (Actemra), from Genentech, Inc. Despite these breakthroughs for scleroderma patients with lung involvement, a significant unmet need exists for treatments for all scleroderma patients, especially to treat the overall disease and halt its progression through achieving remission.

Novel Treatments on the Horizon

Several treatments are in development for scleroderma with various mechanisms of action. In addition to monoclonal antibodies (mAbs), antifibrotic agents and CAR T-cell therapies are under evaluation in several clinical studies across the globe.

CABA-201.

Perhaps the most promising novel approach to treating scleroderma is chimeric antigen receptor (CAR) T-cell therapy, which has traditionally been studied for oncology indications. Multiple CAR T-cell products are in development for scleroderma and other autoimmune diseases. Cabaletta Bio, Inc (Cabaletta), is recruiting ~12 adult participants for an open-label phase I/II study (RESET-SSc) to evaluate the safety and efficacy of CABA-201, a 4-1BB–containing fully human CD19-targeted CAR T-cell investigational therapy, for the treatment of SSc. This trial, which is part of the sponsor's Chimeric Antigen Receptor T cells for Autoimmunity (CARTA) strategy, is evaluating the potential of CABA-201 to "transiently, but fully, eliminate B cells" to potentially enable durable remissions through a "reset" of the individual's immune system, Cabaletta announced in a press release.[5]

In the study, subjects receive a single intravenous infusion of CABA-201 1 x 106 cells/kg following preconditioning with fludarabine and cyclophosphamide. The primary outcome measure is the incidence of adverse events (AEs), and efficacy is one of several secondary endpoints. In January 2024, the sponsor announced that it received fast track designation from the FDA for CABA-201 for the treatment of scleroderma. Then, in March 2024, the agency granted orphan drug designation to the CAR T-cell therapy for the treatment of SSc. The study began in June 2024 and is estimated to complete by July 2029.

FT011.

A novel first-in-class oral therapy, FT011 (asengeprast) from Certa Therapeutics (Certa) is in development for the treatment of chronic fibrosis in multiple organs. The sponsor completed a multinational, double-blind phase II trial that randomly assigned 30 participants to three treatment arms: oral FT011 400 mg, FT011 200 mg, or placebo once daily in addition to the standard of care for 12 weeks. Positive results reported in November 2023 showed a clinically meaningful improvement in 60% of participants treated with FT011 400 mg (p-value = 0.019) and 20% of participants in the FT011 200 mg group compared with 10% in the placebo group.[6] Overall, significant improvements were observed in American College of Rheumatology Composite Response Index in Systemic Sclerosis (ACR-CRISS) score, skin thickness, lung function, physician-reported assessment, and quality-of-life evaluations. FT011 was well tolerated, and no

differences in AE rates were noted between the treatment arms. No serious AEs or AEs resulting in study drug interruption, withdrawal, or discontinuation were reported.

FT011 targets the G protein–coupled receptor GPR68, and transcriptomic research has shown that treatment with FT011 leads to reversal in the activation of genetic markers associated with fibrosis. This provides the potential for a precision therapy, Certa stated.[7] In February 2024, the firm announced that FT011 was granted fast track designation by the FDA for the treatment of SSc after receiving orphan drug designation in October 2023 for the same indication. Following positive results from the phase II study, the sponsor has announced plans to begin a pivotal phase III study in late 2024. The fast-track status of the agent could lead to expedited review of an application through more frequent communication with the FDA, eligibility for accelerated approval and priority review, and a rolling review of the application.

Anifrolumab.

A multicentre, randomised, double-blind, placebo-controlled phase III study (DAISY) is recruiting adult participants with SSc who may be taking one or a combination of protocol-specified standard therapies to evaluate the efficacy and safety of anifrolumab (Saphnelo, from AstraZeneca), a fully human mAb that targets interferon alfa receptor subunit 1. Approximately 306 participants are randomised to receive anifrolumab or placebo subcutaneously once weekly for 52 weeks. The primary outcome measure is the number of participants responding to treatment based on the Revised CRISS. Begun in November 2023, the study is estimated to complete in December 2027.

These treatments are among many other novel therapies under evaluation for the treatment of scleroderma. While early detection and symptom management are paramount for these patients, preventing disease progression and halting the disease altogether have the potential to drastically reduce the number of deaths attributed to scleroderma each year.

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